Formalities

The present Office Action notes that the specification contains sequence information that needed to be in compliance with the provisions for sequence information set forth in 37 C.F.R.§1.821. Applicants respectfully note that the appropriate response was previously filed on 28 July 1994 (possibly paper #6) and should already be of record in this patent application. If this document is not in the PTO's file wrapper, applicants can send substitute copies.

35 U.S.C. §112 Rejections

Claims 63 and 80-82 and 84-90 were rejected under 35 U.S.C. §112 first paragraph as the specification is alleged to not enable a person skilled in the art how to make the claimed invention. On pages 3-4 of the Office Action, the Examiner goes on about all kinds of experiments deemed "necessary" in order to enable the claimed invention, including stringency conditions, hybridization sites and other "magnitude of factors" that are alleged that must be done to develop an antisense oligonucleotide as a pharmaceutical agent. Applicants respectfully traverse this rejection because the Examiner has already deemed the claimed invention "enabled" in the 35 U.S.C. §103 rejection below using a similar (non-prior art) disclosure of applicants in conjunction with known antisense technologies in the art that would have been known to a person skilled in the art.

The claimed invention is a method of treating a condition involving cytokine-mediated toxicity involving using an anti-MIF antisense oligonucleotide or related gene therapy techniques. The Examiner has looked to the specification, in the absence of any knowledge available to a person skilled in the art, to try to determine if there has been sufficient development of a therapeutic antisense agent at the time of the effective filing date to "warrant" enablement, in the opinion of the Examiner. This is not a correct application of a 35 U.S.C. §112 first paragraph rejection. There are two reasons why this rejection is improper. First, the below-discussed 35 U.S.C. §103 rejection provides a combination of references that the same Examiner considered to be enabling to a person of ordinary skill in the art to disclose or suggest the claimed invention. The second reason is that the case law is designed to encourage early disclosure of inventions. The case law, with regard to 35 U.S.C. §112 first paragraph enablement issues, is to avoid imposing arbitrary and unnecessary enablement burdens upon applicants. Applicants do not need to have undergone extensive and expensive product development activities before an Examiner will have enough of his or her questions answered to deem the disclosure "worthy" of an arbitrary enablement standard.

With regard to the first reason, the Examiner already thinks that a person skilled in the art will be aware of Uhlmann et al. (which is prior art to the present invention) and would be aware of how to make and how to use antisense oligonucleotides. The following 35 U.S.C. §103

rejection can be treated as an "admission" by the Examiner of such. Therefore, if the combination of Uhlmann et al. plus the much less than the disclosure in the specification (the specification being much more detailed and extensive than the combination of Clark et al. plus Bernhagen et al.) is enough to disclose the invention to a person of ordinary skill in the art, than this knowledge of Uhlmann plus the specification is sufficient to teach a person skilled in the art how to make and how to use the claimed invention. The Examiner cannot have it both ways.

The rejection does not cite any law or precedent why those detailed disclosures the Examiner deems necessary is required to teach a person skilled in the art how to make or how to use the claimed invention. The Examiner's attention is respectfully drawn to MPEP §2107 wherein the standard for pharmaceutical invention utility and enablement is presented. Further, the Examiner is requiring burdensome and arbitrary demands on the applicant. The Examiner has not pointed to any statute, regulation or precedent for showing that each oligonucleotide much be tested and described in the manner "required" by the Examiner. In fact, just the opposite precedent is supported by public policy considerations.

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public.

*In re Bundy*, 209 USPQ 48 (CCPA 1981).

In addition, it would not serve the public interest to severely limit a claimed invention by requiring massive disclosures just to have a checklist approach to determine how far along in development a particular therapeutic agent may be. This would provide claims of such limited scope that it would be too easy for an infringer to circumvent.

> The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

*In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

In summary, the Examiner has admitted that a person skilled in the art is fully enabled to practice the claimed invention using teachings available in the art at the time of the effective filing date plus the specification. Further, this rejection imposes an arbitrary and unsupported standard of enablement that would require a particular product to have undergone more extensive product development activities, in contravention to public policy standards designed to encourage early disclosure of inventions. Accordingly, the specification is fully enabled to a person skilled in the art at the time of the effective filing date.

Claims 63, 80-82 and 84-90 were rejected under 35 U.S.C. §112 second paragraph as indefinite in failing to describe the MIF term. Applicants have amended claim 63 to provide for a full written description of MIF (Migration Inhibitory Factor) in claim 63 with the MIF term in parentheses following, such that dependent claims can continue to employ the MIF language. Applicants submit that this format is appropriate to address the Examiner's concern.

35 U.S.C. §103 Rejection

Claims 63, 80-82 and 84-90 were rejected under 35 U.S.C. §103(a) as unpatentable over Berhagen et al. in view of Uhlmann et al. and Clark et al. The rejection is based upon the combination of Berhagen et al. which is the primary reference disclosing the beneficial effects of inhibition of MIF, especially by showing the rise in MIF levels in LPS-dosed mice. Uhlmann et al. was applied to show that a person or ordinary skill in the art is enabled how to make and use antisense oligonucleotides, and ribozyme and triple helix therapy. Lastly, the secondary reference, Clark et al., provides a disclosure of one variant of an MIF sequence. The conclusion is that the required motivation to combine is contained in Berhagen et al. wherein the activity of a MIF inhibitor is provided. Applicants submit that the foregoing rejection is moot because Berhagen et al. is not prior art.

The Declaration and Power of Attorney form indicates that the present patent application claims priority from U.S. patent application 08/063,399 filed on 17 May 1993 under 35 U.S.C. §120. Therefore, although the filing receipt incorrectly does not so note this priority, the specification was amended in Amendment A (paper 21 filed on 13 June 1997) to so note the priority of this continuation-in-part (CIP) patent application. It should be further noted that the effective filing date of the subject matter of this patent application is 17 May 1993 because the specification of parent patent application Serial Number 08/063,399 supports the presently claimed invention (please see pages 26-31 of the USSN 08/063,399 patent application).

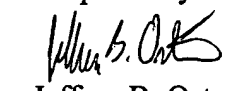
Bernhagen et al. was published on 21 October 1993 according to the date printed on this reference. Therefore, Bernhagen et al. was published after the effective priority date of the

subject matter of the claimed invention and is not prior art. Accordingly, the only references that can be used in a 35 U.S.C. §103(a) rejection are the two secondary references.

This leaves Uhlmann et al. showing a person of ordinary skill in the art how to make and how to use antisense oligonucleotides and Clark et al. showing the initial cloning of MIF. The combination of both secondary references (if they can be combined) does not provide a requisite showing of any motivation to want to inhibit MIF activity through antisense means. Moreover, there is no motivation to combine these two references because there is no suggestion in Clark that a therapeutic agent would be useful that inhibits MIF activity through antisense means. Accordingly, when Bernhagen et al. is no longer part of the rejection, the remaining secondary references cannot be combined with each other, and if they were combined, do not suggest the claimed invention. Withdrawal of this rejection is respectfully requested.

In view of the foregoing remarks, applicants respectfully request withdrawal of the rejections, and allowance of pending claims 63, 80-82 and 84-90.

Respectfully submitted,



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